UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/863,158	05/23/2001	David J. Ecker	ISIS-4766	9473

32650 7590 09/10/2004

WOODCOCK WASHBURN LLP
ONE LIBERTY PLACE - 46TH FLOOR
PHILADELPHIA, PA 19103

EXAMINER	
SODERQUIST, ARLEN	
ART UNIT	**PAPER NUMBER**
1743	

DATE MAILED: 09/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/863,158	ECKER ET AL.
	Examiner	Art Unit
	Arlen Soderquist	1743

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-42,52 and 53* is/are pending in the application.

4a) Of the above claim(s) *52 and 53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7-9-01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. Applicant's election with traverse of Group IIA in the reply filed on June 14, 2004 is acknowledged. The traversal is on the ground(s) that the examination of either set of claims will reveal background art relevant to the other group and there would not be an undue burden on the examiner. This is not found persuasive because there are some distinct differences between the two sets of claims that amount to difference in the search required which amount to a burden. The standard is not is there some overlap in the search but is there enough overlap that one could reasonably expect a search of one of the methods to cover the search for the second method. That is not the case in this instance. Group IIA requires the chemical reactant species to be jetted while Group IIB only requires that they are transported under control of a control means. Group IIA does not require a control means and could include methods in which the reactants are transported by hand (not a required search for Group IIB). In distinction to this Group IIB does not require any particular structure for the dispenser and automated pipettes are a required search (not a required search for Group IIA). Group IIA also does not place any restrictions on the type support and a search in nonporous supports is required. Group IIB on the other hand requires a support through which the sample is transported (is porous?) and a search in non porous supports is not required. These differences allow for the possibility that the claims in the two groups could further diverge during prosecution. It is noted that a similar restriction was made in Application 08/778,876, a parent of the instant application and the claims of Group IIB were elected at that time. After prosecution, claims 1-11 of US Patent 5,925,732 resulted. Even though these issued claims were narrowed to be within the scope of the claims in Group IIA, the broader claims would not have been rejoined unless the reason the issued claims were allowable was because of the scope of the claims in Group IIA.

The requirement is still deemed proper and is therefore made FINAL.

2. The disclosure is objected to because of the following informalities: the current status of the continuity data needs to be updated and the title of the invention is not descriptive of the claimed invention.

Appropriate correction is required.

3. Claims 26-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The preamble of claim 27 states a method for synthesizing a chemical species yet

there is no clear step or indication that a reaction occurs between any of the first and second chemical reactant species. Thus it appears that these claims are simply claiming a method of distributing reactants to reaction sites on a surface.

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

5. Claims 26-27, 29, 32, 35-40 and 42 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Nishioka (US 5,449,754) or Baldeschwieler (US 5,847,105).

In the patent Nishioka teaches ink-jet printing technology applied to the creation of multi unit chemical compound libraries. Ink-jet type nozzles are used to inject multiple droplets onto the surface an appropriate support, such droplets consisting of solutions containing units of the chemical compound that will attach (bond) to the support surface. Droplets are then injected, by the nozzles, onto the support to react with the first attached unit of the chemical compound. The second step is repeated to create multiple varying unit chemical compounds. Ink-jet printing technology allows the deposition of small droplets that do not overlap or splatter. The system is particularly useful in the creation of libraries of multiple peptide compounds where the units are amino acids. Column 2, line 46 to column 3, line 7-69 call this method SCAMP (Synthesis of Combinatorial Arrays by Microjet Printing) and teach that a support, such as an aminated glass slide, filter or membrane, is placed on a vibration-free platform. A print head is mounted to precision xy translators above the sample. The print head scans the sample, depositing small droplets (typically 0.1 μg) of coupling solution onto programmed sites on the support. The

activated coupling solutions may be similar to those used in commercial peptide synthesizers and will result in a protected amino acid binding to the support. The print head will preferably contain a minimum of 20 orifices, so that at least 20 different solutions can be injected onto the support in one pass. Typically, each orifice will inject a particular amino acid onto the support. After the first scan, a single layer of amino acids will be bound to the support at programmed sites. The support is then washed, deprotected and then washed again. The scan, wash, and deprotection steps are repeated as often as desired, resulting in the synthesis of immobilized peptides at the programmed sites. The final step is removal of side-chain blocking groups. An example of how this would occur is found in columns 5-6.

In the patent Baldeschwieler teaches method and apparatus for performing multiple sequential reactions on a matrix. In the method a substrate is prepared upon which microdrop-sized loci are located at which chemical compounds are synthesized or diagnostic tests are conducted. The loci are formed by applying microdrops from a dispenser from which a microdrop is pulse fed onto the surface of the substrate. Column 1 lines 14-25 teach that the apparatus and method are useful for performing a test or synthesis involving sequential steps such as DNA sequencing, DNA diagnostics, oligonucleotide and peptide synthesis, screening tests for target DNA, RNA or polypeptides, synthesis of diverse molecules, DNA separation technology whereby DNA binds to target molecules, preparation of polysaccharides, methods for making complementary oligonucleotides, and any other test, sequencing or synthetic method utilizing a sequence of steps at a locus. An advantage or improvement can be obtained by providing loci so that combinations of different reactions may be conducted on the same matrix. The summary of column 2 teaches how the synthesis steps are performed. In the case of delivery of reagents that become attached to the surface, the invention provides a substrate having a surface to which a first reagent can be attached by dispensing microdrops of the reagent in liquid form onto the substrate. The dispenser is displaced relative to the surface and at least one microdrop is applied thereto containing the same or a different reagent. By repeating this using the same or a different first reagent in liquid form, a plurality of loci on the surface may be prepared wherein the reagents covalently attach at microdrop-sized loci wherein the boundaries of each locus are not contiguous to any adjacent locus. The surface may then be washed to remove unattached reagent. If needed, the entire surface may be treated, or alternatively, a

selected subset of loci may be treated, with deprotecting reagents to expose reactive sites of the molecules attached to the surface. The deprotecting reagent may also be dispensed from the device. Then one or more microdrops containing a second reagent in liquid form may be dispensed at selected loci on the substrate surface, whereby the second reagent is selected to react with the molecules already attached to the matrix. The dispenser is again displaced relative to the surface to apply the second reagent at different loci using the same or a different second reagent which reacts with the respective attached molecules. Again, the entire surface will be washed to remove unreacted second reagents. Then the entire surface or selected subsets of loci may be treated with deprotecting agents, and this process may be repeated. Column 3, lines 27-33 teach the substrate as a solid, such as glass, prepared to receive linkers attached to the surface. Porous substrates, such as paper or synthetic filters may be used, as well as filters having straight, parallel micropores. In such a microporous substrate, the reactions may take place within the pores, thus amplifying the potential signal at the locus. Column 6 lines 46-67 discuss the ink-jet used to dispense the microdroplets.

6. Claims 26, 35-40 and 42 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Brennan (US 5,474,796) or Winkler (US 5,677,195).

In the patent Brennan teaches method and apparatus for conducting an array of chemical reactions on a support. Column 2, lines 11-18 teach that the invention provides a method for conducting a large number of chemical reactions on a support surface. Solutions of chemical reactants are added to functionalized binding sites on the support surface by means of a piezoelectric pump. This pump deposits microdroplets of chemical reactant solution onto the binding sites. The chemical reactant at each binding site is separated from the others by surface tension. Columns 5-6 and example 3 discuss the piezoelectric impulse jet pump and example 2 shows how the oligonucleotides are assembled (synthesized) on an array plate.

In the patent Winkler teaches combinatorial strategies for polymer synthesis. Column 1, lines 12-20 teach that the invention is directed to the field of polymer synthesis and screening. In one embodiment a method and system for synthesizing arrays of diverse polymer sequences is taught with a specific aspect being the synthesis of diverse polymer sequences such as peptides or oligonucleotides. The diverse polymer sequences may be used, for example, in screening studies for determination of binding affinity. Column 2, lines 15-31 teach methods and devices

for delivering (and, in some cases, immobilizing) available libraries of compounds on specific regions of a substrate. In preferred embodiments, various monomers or other reactants are delivered to multiple reaction sites on a single substrate where they are reacted in parallel. According to a preferred embodiment of the invention, a series of channels, grooves, or spots are formed on or adjacent a substrate. Reagents are selectively flowed through or deposited in the channels, grooves, or spots, forming an array having different compounds--and in some embodiments, classes of compounds--at selected locations on the substrate. Relative to the compounds formed at spots on the substrate, column 3 lines 12-24 teach a first monomer solution is spotted on a first set of reaction regions of a suitably derivatized substrate. Thereafter, a second monomer solution is spotted on a second set of regions, a third monomer solution is spotted on a third set and so on, until a number of the regions each have one species of monomer located therein. These monomers are reacted with the surface, and the substrate is subsequently washed and prepared for reaction with a new set of monomers. Dimers, trimers, and larger polymers of controlled length and monomer sequence are prepared by repeating the above steps with different groupings of the reaction regions and monomer solutions. Monomers are defined in the paragraph bridging columns 4-5. The substrate is defined in column 6, lines 49-60. Additional discussion of the spotting embodiments is found in column 9 line 59 to column 10 line 13 and columns 18-20. this discussion includes the use of a pipette or ink-jet printer to dispense droplets of reactant onto predefined regions (sites) of the substrate in an iterative manner.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. Claims 28,30-31, 33-34 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nishioka or Baldeschwieler as applied to claims 26-27, 29, 32, 35-40 and 42 above, and further in view of the admitted state of the prior art, Koester (US 4,923,901) and Salmon. Column 3, lines 4-14 of Baldeschwieler discuss the removal of the formed compounds either selectively or non-selectively for diagnostic assays or isolation of the final compound(s). Neither reference teaches all of the claimed supports or using a collection plate to collect the synthesis products.

Page 15, line 22 to page 16, line 3 of the instant specification teach that several of the possible support are either known or commercially available. Specifically, supports include CPG (controlled pore glass) available from various distributors including CPG Inc./Millipore Corp.; RAPP copolymer, a highly crosslinked polystrene, sold as TentaGel or a like product HLP (high loaded polystrene) sold by ABI Corp.; Primer Support, a highly crosslinked polystrene, sold by Pharmacia; POROS-OS polystrene sold by PerSeptive, MPG (a magnetic pore glass) sold by CPG Inc.; Nucleic Acid Membrane Support sold by Millipore. Other useful supports include membranes sold by the Amicon division of W. R. Grace, Inc., and those sold by Gelman Sciences. Other membrane supports include membranes as described or referenced in U.S. Pat. No. 4,923,901 (Koester) assigned to Millipore Corp.; various supports as described in patent application WO 94/05394 and references cited therein; and various supports as described in patent application WO 90/02749 including activated polystrene layer on a polyethylene membrane.

The Koester patent was sited in the instant specification as disclosing supports usable for the instant methods. More specifically Koester teaches a method for synthesizing oligonucleotides and peptides directly onto a membrane. The method provides a means for generating membrane affinity supports. A modified membrane for the method of direct synthesis is also provided. The introduction of the patent teaches various supports that are known to be used in solid phase peptide and oligonucleotide synthesis. These supports include beaded material such as cellulose, glass beads, Sephadex, Sepharose, agarose, polyacrylamide, porous

particulate alumina, hydroxyalkyl methacrylate gels, diol-bonded silica or porous ceramics, flat material such as filter disc of nylon and nitrocellulose, glass beads of controlled porosity. A membrane, a being flat and highly porous, mechanical stable material, would be most advantageous as affinity support, because it could be handled easily, cut into various sizes, stacked on top of each other for upscaling purposes and reused several times. Furthermore, the support should be chemically stable under the conditions of oligonucleotide and peptide synthesis and should not show non-specific binding of either nucleic acids or proteins as this would give rise to a sensitivity-reducing background interaction. The membranes of Koester are taught as fulfilling these requirements or providing these advantages.

In the paper Salmon teaches discovery of biologically active peptides from a library synthesized on solid supports. Pages 11709 and figure 3 teach the two-stage release of the peptide from the support for testing purposes. In the method a plurality of beads is first added to wells (donor chambers) of a 96-well microassay filtration plate. A portion of the bound peptide is released from the support and transferred from the filtration plate to a corresponding assay plate (acceptor chambers) and reagent is added. The beads from wells that a reaction with the reagent occurred are then individually loaded into wells of a microassay filtration plate and the additional peptide is released, transferred to a corresponding assay plate and a reagent added. In the paragraph bridging pages 11711 and 11712 Salmon teaches fluid volumes for the wells can be in the range of 10 - 100μl.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the admitted known synthesis supports or those of Koester into the methods of Nishioka or Baldeschwieler because of the known advantages of the porous supports as taught by Koester. It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate a collection or assay plate into the methods of Nishioka or Baldeschwieler because of the ability to carry out further tests on the synthesized materials or to isolate the individual compounds for analysis as taught by Salmon and Baldeschwieler.

9. Claims 27-34 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brennan or Winkler as applied to claims 26, 35-40 and 42 above, and further in view of the admitted state of the prior art, Koester (US 4,923,901) and Salmon all secondary references as explained above. Neither reference teaches porous supports or using a collection plate to collect

the synthesis products. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the admitted known porous synthesis supports or those of Koester into the methods of Brennan or Winkler because of the known advantages of the porous supports as taught by Koester. It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate a collection or assay plate into the methods of Brennan or Winkler because of the ability to carry out further tests on the synthesized materials or to isolate the individual compounds for analysis as taught by Salmon.

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 26-42 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 5,925,732. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims totally encompass the patented claims and one could not practice the patented invention without infringing the instant claims.

12. The information disclosure statement filed July 9, 2001could not be totally considered by the examiner because a legible copy of each publication or that portion which caused it to be listed was not readily available to the examiner. As a result those items have not been considered but will when they become available to the examiner.

13. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The additionally cited art are patents in the same patent family and those related to biopolymer synthesis.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arlen Soderquist whose current telephone number is (571) 272-1265 as a result of the examiner moving to the new USPTO location. The examiner's schedule is variable between the hours of about 5:30 AM to about 5:00 PM on Monday through Thursday and alternate Fridays.

A general phone number for the organization to which this application is assigned is (571) 272-1700. The fax phone number to file official papers for this application or proceeding is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

September 9, 2004
ARLEN SODERQUIST
PRIMARY EXAMINER